Docket No.: AM 101333
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Wumin Li et al.

Application No.: 10/796,925	Confirmation No.: 3270
Filed: March 10, 2004	Art Unit: 1645
For: ADJUVANTED BOVINE VACCINES	Examiner: Lakia J. Tongue

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

A Notice of Appeal for the above-identified application was filed on March 31, 2009 with a Pre-Brief Conference Request. A Pre-Brief Conference decision was mailed on May 26, 2009. Pursuant to § 41.37(a) an Appeal Brief was due May 31, 2009. Pursuant to § 41.37(c), a request for a five-month extension-of-time under § 1.136(a) and the required fee are submitted herewith, to extend the period for filing an Appeal Brief to October 31, 2009. Because Oct. 31 was a Saturday, the period for filing the Appeal Brief is extended to the next business day, November 2, 2009.

The fees required under §§41(b)(2) and 1.136(a) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is, Pfizer, by virtue of a merger that closed on October 15, 2009, between Pfizer and Wyeth, the assignee of the entire right, title and interest in the subject application from each of the inventors that was recorded on March 10, 2004 at Reel 015091 Frame 0765.

II. RELATED APPEALS AND INTERFERENCES

There are no prior or pending appeals, interferences, or judicial proceedings known to the Appellant which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 3 claims pending in the application.

B. Current Status of Claims

1. Cancelled: 1-21
2. Withdrawn from consideration but not cancelled: None
3. Pending: 22-24
4. Allowed: None
5. Rejected: 22-24
6. On Appeal: 22-24

IV. STATUS OF AMENDMENTS

Applicants filed an Amendment and Reply to a Non-Final Office Action on October 14, 2009 in which no claim amendments were made. Applicants responded to the Final Office Action mailed on January 7, 2009, by filing a Notice of Appeal and a Pre-Brief Conference Request. All amendments to the claims have been entered and are reflected in the list of claims in Appendix A.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 22 is directed to a method for reducing shedding of *E. coli strain* O157:H7 in an animal by administering an adjuvanted vaccine composition. *See*, for example, specification at page 1, lines 6-9. The vaccine composition comprises inactivated or killed whole *E. coli* O157:H7, aluminum hydroxide and an adjuvant. Specification, page 3, lines 2-5. The adjuvant is an oil emulsion and comprises 1% to 3% vol/vol (v/v) of polyoxyetheylene-polyoxypropylene block copolymer, 2% to 6% v/v of squalane, 0.1% to 0.5% v/v of polyoxyethylene sorbitan monooleate, and buffered salt solution. Specification at page 4, lines 3-10. The vaccine is administered in an effective amount by parenteral injection. Specification at page 7, lines 18-25 and Example 2 (vaccination by subcutaneous injection). The vaccine optionally includes a pharmaceutically acceptable carrier. Specification at page 6, lines 25-32 and original claim 1.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 22 and 24 are unpatentable under 35 U.S.C. 103(a) over Johnson et al., "Effect of vaccination of dairy calves with an inactivated *E. coli* O157:H7 bacterin on shedding of *E. coli* O157:H7," Food and Environmental Safety Posters, 1999, Abstract 40aP ("Johnson"), in view of Saito et al., U.S. 2005/0158330 A1 ("Saito"), and Baylor et al., *Vaccine*, 2002, 20:S18-S23 ("Baylor").

2. Whether claims 22-24 are unpatentable under 35 U.S.C. 103(a) over Johnson in view of Saito, Baylor and Elder et al., *J. Animal Sci.*, 2002, 80 (sup. 1):151 (abstract 602) ("Elder").

VII. ARGUMENT

A. BACKGROUND

The claims on appeal are directed to a method for reducing shedding of *E. coli* strain O157:H7 in an animal by parenterally injecting a vaccine composition comprising inactivated or killed whole *E. coli* O157:H7, an adjuvant having the composition set out in claim 22, and aluminum hydroxide. *See* claim 22. The application discloses that *E. coli* O157:H7 is a bacterium that colonizes the gut of bovine species (among other species) and is a human pathogen that infects humans, primarily through ingestion of contaminated beef. Specification at page 1, lines 11-19. An important route of *E. coli* O157:H7 contamination of beef is the shedding of *E. coli* O157:H7 into the feces of colonized animals, subsequent contamination of beef during processing and slaughtering, and ingestion of contaminated beef. *Id.* and page 2, lines 1-9. Various methods have been attempted to reduce the level of *E. coli* O157:H7 contamination, including by immunizing animals to prevent *E. coli* O157:H7 shedding. *Id.* at 3-6.

According to the specification, "it remains a challenge to produce a vaccine to effectively prevent *E. coli* O157:H7 colonizations in ruminant animals, particularly bovines, that can be passed through their carcasses into the human food supply." Specification at page 2, lines 31-33. Such challenges include the problem that a live bacterial vaccine may potentially be unsafe, whereas a killed or inactivated vaccine may fail to stimulate an effective immunologic response and that adjuvants used to stimulate an immunological response may have undesirable consequences. Specification at page 3, lines 25-30. Additionally, because the beef of vaccinated animals is ultimately sold to consumers, "it is highly desirable to minimize injection site reactions which adversely impact the meat quality of an animal which is sold for food consumption." Specification at page 3, line 33 though page 4, line 2.

Appellants' claimed invention addresses the problem of providing effective vaccination of animals that reduces shedding of *E. coli* O157:H7 in colonized animals without adversely affecting meat quality by providing for vaccinating animals with a combination of dead or attenuated *E. coli* O157:H7, the adjuvant recited in claim 22, and aluminum hydroxide. Example 2 of the specification and a Declaration of Under 37 C.F.R. §1.132 from co-inventor Wumin Li ("the Li Declaration," attached in Evidence Appendix B) set out a comparison of a vaccine according to

the claimed invention and a vaccine formulated with the adjuvant, aluminum hydroxide.[1] The results set out in Example 2 and the Li Declaration demonstrate that a vaccine according to the invention comprising the SP oil adjuvant and aluminum hydroxide results in a significantly higher immune response, compared to aluminum hydroxide alone but with similar rates of injection site reactions. The Li Declaration sets out that it was unexpected that the claimed composition of a metabolizable oil (i.e., SP Oil) plus aluminum hydroxide had a significant improvement in titers versus the standard adjuvant (aluminum hydroxide) and, additionally, that it was unexpected that the size of the reaction lump at the site of injection was the same for aluminum hydroxide alone and for the vaccine according to the invention that had such a significantly higher titer. Appendix B, Li Declaration at page 5.

Example 3 of the specification describes a field study performed to compare the effectiveness of various interventions to reduce the prevalence of *E. coli* in feedlot cattle. The results of the study showed that a vaccine according to the invention reduced *E. coli* O157 prevalence by 20.3% on hide samples and by 31.1% in fecal samples and that, when combined with other intervention strategies, e.g., *L. acidophilis* or neomycin feed supplement, the vaccine provided additional reduction in antigen shedding.

The Examiner asserts that claims 22 and 24 are obvious over Johnson in view of Saito and Baylor and claims 22-24 are obvious over Johnson in view Saito, Baylor, and Elder "because all the claimed elements were known to in the prior art and one skilled in the art could have combined the elements as claimed with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention." *See*, e.g., Final Office Action mailed January 7, 2009 at page 8, second paragraph. The Examiner also asserts that the Li Declaration is not persuasive because the claims are drawn to a combination of SP and aluminum hydroxide, whereas "the Li declaration compares their [sic] adjuvant to aluminum hydroxide, which is insufficient because the adjuvant compared in the

[1] Example 2 of the specification is written in the present tense and is thus a prophetic example. The Li Declaration, is written in the past tense and thus describes work as it was performed and results that were obtained. Notwithstanding that Example 2 is a prophetic example and the Li Declaration reports on a study that was conducted, Example 2 and the Li Declaration set out identical methods and "results." Thus, notwithstanding that Example 2 is set out in prophetic terms and the Li Declaration reports on work that was performed and results obtained, the respective disclosures of Example 2 and the Li Declaration are believed to be the same, and are thus interchangeable.

declaration is vastly different than metabolizable oil adjuvants or 'SP Oil' as claimed." Final Office Action mailed January 7, 2009 at page 3-4, bridging paragraph.

The rejections should be withdrawn because the Examiner has committed the following errors:

(i) The Examiner has culled selective teachings from the prior art and thus failed to properly ascertain the scope and content of the prior art;

(ii) The Examiner has improperly failed to give weight to the Li Declaration because she has required that a comparison between the claims and applicants invention, rather than the prior art.

B. LEGAL PRINCIPLES

"During examination, the examiner bears the initial burden of establishing a prima facie case of obviousness." *In re Kumar,* 418 F.3d 1361, 1366 (Fed. Cir. 2005). In so doing, the Examiner must make the factual determinations set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966): (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. "Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert,* 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). Claims are likely to be unobvious "when the prior art teaches away" from their practice. *KSR Int'l. Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007). Evidence rebutting a *prima facie* case of obviousness must be considered. *In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007).

C. ANALYSIS

1. The Examiner Has Failed to Properly Consider the Scope and Content of the Prior Art and Differences Between the Prior Art and the Claimed Invention

a. The Examiner misinterprets Johnson and fails to properly ascertain the differences between Johnson and the claimed invention

The Examiner first errs by failing to consider Johnson as a whole. Johnson discloses vaccination of newly weaned dairy calves by intramuscular injection of inactivated *E. coli* O157:H7

bacterin, supplemented with inactivated verotoxin 2 (VT2) and adherence factor, $intimin_{O157}$. Control and experimental animals were treated and then challenged with antibiotic resistant inactivated *E. coli* O157:H7. Johnson reports that shedding of *E. coli* O157:H7 bacteria in feces fell in both vaccinated and control animals within 2-3 weeks of challenge. Johnson discloses that the results obtained "indicate that infection of naturally-reared weaned dairy calves by *E. coli* O157:H7 is frequently transient...and is unlikely to be controlled by immune responses induced by parenterally administered inactivated bacterins."

The Examiner characterizes Johnson by describing the results as set forth above and then concluding, "Johnson et al. does not specifically disclose an adjuvant comprising SP Oil and aluminum hydroxide." *See*, e.g., Final Office Action dated January 9, 2009 at page 7, first two full paragraphs and Non-Final Office Action dated September 16, 2008 at page 6, bottom through page 7, first full paragraph. The Examiner's clipped characterization of Johnson does not completely nor fairly ascertain the scope and content of Johnson, nor the differences between Johnson and the claimed invention. Thus, implicit in the Examiner's characterization is that Johnson discloses an "effective amount" of a vaccine composition for "reducing shedding of *E. coli* O157:H7 in an animal," as recited in claim 1. Such implicit characterization is not correct. Johnson discloses explicitly that there was "little difference" in levels and duration of shedding in vaccinated versus control animals. Johnson thus fails to disclose an "effective amount" of a vaccine for reducing shedding of *E. coli* O157:H7.

The Examiner's consideration of Johnson, moreover, fails to address Johnson's explicit statement that infection of naturally-weaned dairy calves by *E. coli* O157:H7 "is unlikely to be controlled by immune responses induced by parenterally administered inactivated bacterins."

b. The Examiner fails to consider disclosure in Baylor that is inconsistent with the claimed invention

The Examiner has a similarly selective reading of Baylor. The Examiner states that, "Baylor et al., was used solely as an evidentiary reference to demonstrate that aluminum hydroxide has been commonly used as an adjuvant in many vaccines for decades and have [sic] been proven safe." *See,* e.g., Final Office Action mailed January 7, 2009 at pages 6-7, bridging paragraph. Baylor teaches, however, that aluminum adjuvants "have been associated with severe local reactions

such as erythema, subcutaneous nodules and contact hypersensitivity." Baylor at Abstract and page S20, column 2, lines 1-4. As set out in the instant specification and discussed above, site reactions, such subcutaneous nodules, adversely affect meat quality and are thus to be minimized. The Examiner, however, takes no notice of Baylor's explicit teaching that aluminum adjuvants are known to be associated with such "severe local reactions."

c. The Examiner mischaracterizes Saito and fails to consider Saito has a whole

The Examiner similarly errs by both mischaracterizing Saito and failing to consider Saito as a whole. The Examiner first mischaracterizes Saito as disclosing "using aluminum hydroxide in the disclosed composition (see paragraphs 0101 and 0109)." *See,* e.g., Final Office Action dated January 7, 2009 at page 6. This statement is not correct. Saito does not disclose a combination of aluminum hydroxide and the water-in-oil-in-water (W/O/W) adjuvants that are the subject of Saito's invention. Saito only mentions aluminum hydroxide in the context of being used by itself in comparative control vaccine compositions. Saito never states or suggests that aluminum hydroxide could or should be used in such W/O/W adjuvants. *See* Amendment filed October 14, 2008 at page 3, bottom paragraph through page 4, second full paragraph.

The Examiner, moreover, refuses to consider portions of Saito that would have discouraged a person of ordinary skill in the art from using aluminum hydroxide in an oil emulsion vaccine composition. Table 6 of Saito, for example, compares the "effectiveness" of various Er formulations (expressed in terms of PD_{50}). An aluminum gel-adjuvanted formulation produced a PD_{50} of 77.1, whereas experimental oil emulsion vaccines produced PD_{50} values as high as 2660.1 (*see* "Vaccine 1"). Similarly, in the Mycoplasma experiments summarized in Table 8, the aluminum hydroxide-adjuvanted formulations performed much worse than the W/O/W formulations as measured by lesion score and percent decrease in lesions. According to Saito, "the aluminum gel vaccine did not at all show a lesion-decreasing effect by the vaccine, irrespective of the presence or absence of PEG addition." *See* paragraph [0112], last sentence. A skilled person having knowledge of the dismal performance of the aluminum hydroxide gel as an adjuvant, as reported by Saito, would have been highly discouraged from using aluminum hydroxide in combination win an oil emulsion vaccine formulation.

d. In failing to consider the prior art as a whole, the Examiner ignores or fails to give weight to disclosure that that teaches away from the claimed invention and fails to acknowledge the differences between the prior art and the claimed invention

The Examiner's failure to consider the complete content of Johnson, Saito and Baylor is legal error. A prior art reference must be considered as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983); *In re Hedges,* 783 F.2d 1038, 1041 (Fed. Cir. 1986) ("[T]he prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill."). It is thus, "impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" *Id.* (*quoting In re Wesslau,* 353 F.2d 238, 241 (CCPA 1965)). The Examiner has, in particular, failed to consider content in Johnson, Saito and Baylor that teach away from the claimed invention. *In re Kahn,* 441 F. 3d 977, 990 (Fed. Cir. 2006), *quoting In re Gurley,* 27 F.3d 551, 553 (Fed. Cir. 1994). ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.") In the absence of considering the portions of the prior art that would discourage one of ordinary skill in the art to make the claimed invention, the Examiner cannot properly conclude the claims are *prima facie* obvious over the prior art.

The Examiner's failure to appreciate or acknowledge that Johnson fails to disclose any reduction in the shedding of *E. coli* O157:H7 following vaccination leads to a failure to fully ascertain the differences between the prior art and the claimed invention. The Examiner thus fails to ascertain that a difference between the prior art and the claimed invention is the administration of an amount of vaccine that is effective in reducing shedding of *E. coli* O157:H7. In the absence of properly ascertaining the differences between the prior art and the claimed invention, the Examiner cannot properly conclude the claims are *prima facie* obvious over the prior art.

2. The Examiner has improperly failed to give weight to the Li Declaration because she has required a comparison between the claims and Applicants' invention, rather than the prior art

The rejections should also be withdrawn because the Examiner has failed to give proper consideration to the Li Declaration. As set out above, the Li Declaration sets out that is was unexpected that the claimed composition of a metabolizable oil (*i.e.,* SP Oil) plus aluminum hydroxide had a significant improvement in titers versus the standard adjuvant (aluminum hydroxide) and, additionally, that it was unexpected that the size of the reaction lump at the site of injection was the same for aluminum hydroxide alone and for the vaccine according to the invention that had such a significantly higher titer. Appendix B, Li Declaration at page 5. The Examiner failed to give due consideration to the Li Declaration on the grounds that the claims are drawn to a combination of SP and aluminum hydroxide, whereas "the Li declaration compares their [sic] adjuvant to aluminum hydroxide, which is insufficient because the adjuvant compared in the declaration is vastly different than metabolizable oil adjuvants or 'SP Oil' as claimed." Final Office Action mailed January 7, 2009 at page 3-4, bridging paragraph. The Examiner's failure to consider the Li Declaration is legal error because in essence it requires a showing of unexpected results by comparing the claimed invention to itself, rather than the closest prior art.

Unexpected results are shown by comparing the claimed invention to the closest prior art. *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1370 (Fed. Cir. 2007) (*citing Kao Corp. v. Unilever United States, Inc.,* 441 F.3d 963, 970 (Fed. Cir. 2006) and *In re Baxter Travenol Labs.,* 952 F.2d 388, 392 (Fed. Cir. 1991), *reh'g & reh'g en banc denied,* 488 F.3d 1377, 2007 U.S. App. LEXIS 11886 (Fed. Cir., 2007), *cert denied,* 127 S. Ct. 2967, 2007 U.S. LEXIS 7522 (U.S., 2007). The claimed invention may alternatively be compared to closer prior art than cited by the Examiner. *See* MPEP 716.02(3), references omitted. However, "applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." *Id., citing in re Geiger,* 815 F.2d 686, 689 (Fed. Cir. 1987) (Newman, J., concurring). Requiring a comparison between the claimed invention and the combination of references used to reject the claims under section 103 "would be requiring comparison of the invention with the results of the invention." *Id., citing in re Chapman,* 357 F.2d 418, 422 (CCPA 1966).

Here, the claimed invention is a method for reducing shedding of *E. coli* strain O157:H7 in an animal by parenteral administration of an effective amount of a composition comprising inactivated or killed whole *E. coli* O157:H7, aluminum hydroxide the recited SP oil adjuvant in a buffered salt solution. The prior art cited by the Examiner fails to show a vaccination with a vaccine comprising *E. coli* O157:H7 with either of SP or aluminum hydroxide. Johnson, the primary reference relied upon by the Examiner and the only cited reference that even mentions *E. coli* O157:H7, discloses vaccination without any adjuvant. In comparing the claimed invention combining *E. coli* O157:H7, SP oil and aluminum hydroxide to compositions comprising *E. coli* O157:H7 and aluminum hydroxide, the Li Declaration shows unexpected results of the claimed invention to a composition that is closer than the prior art cited by the Examiner. No more is required. It is thus legal error for the Examiner to find the Li Declaration "insufficient because the adjuvant compared in the declaration is vastly different than metabolizable oil adjuvants or 'SP Oil' *as claimed*." Final Office Action date January 7, 2009 at page 4 (italics added). The Examiner has improperly required the Applicant to show unexpected results by comparing the claimed invention to itself and consequently erred in failing to give due consideration to the unexpected results reported in the Li Declaration. The Li Declaration, in fact, shows that the claimed invention provides unexpected results over the prior art. For this additional reason the rejections should be withdrawn.

3. The Examiner Has Failed to Provide a Legitimate Rationale for a Reasonable Expectation in Combining the Prior Art to Arrive at the Claimed Invention

The Examiner's failure to properly consider the scope and content of the prior art results in an improper rationale for combining the prior art to arrive at the claimed invention. The Examiner thus asserts that:

> It would have been expected, barring evidence to the contrary, that the composition would be effective in reducing shedding of *E. coli* O157:H7 because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.
>
> Final Office Action dated January 7, 2009 at page 8.

The Examiner's rationale is misplaced on a number of fronts. First, Johnson reports that a vaccine comprising *E. coli* O157:H7 did not have a significant effect on shedding of bacteria. Thus Johnson provides explicit "evidence to the contrary" that, at the time the invention was made, one of ordinary skill in the art would have a reasonable expectation that the claimed composition would be effective in reducing shedding of *E. coli* O157:H7. Additionally, both Saito and Baylor disclose explicitly that vaccines comprising aluminum hydroxide are known to cause lesions at the injection site. Thus, contrary to the Examiner's assertion, the claimed combination leads to a change in the "function" of aluminum hydroxide by reducing injection-site lesions and it would not be predictable that the claimed combination could predictably lead to such a result.

4. The Examiner Has Used the Applicant's Claims and Hindsight Reconstruction as Motivation to Combine the Prior Art

It is axiomatic that the Examiner may "not use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch,* 972 F.2d 1260, 1266 (Fed. Cir. 1992) (internal citations omitted). It is improper, in determining whether a person of ordinary skill would have been led by the combination of references, simply to "[use] that which the inventor taught against its teacher." *In re Lee,* 277 F.3d 1338, 1343 (Fed. Cir. 2002), *citing W.L. Gore v. Garlock, Inc.,* 721 F.2d 1540, 1553 (Fed. Cir. 1988) ("[t]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure").

In KSR, the Supreme Court cautioned that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon ex post reasoning." *KSR,* 550 U.S. at 421 (*citing Graham v. John Deere Co.,* 383 U.S. 1, 36 (1966)). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l. Co. v. Teleflex Inc.,* 550 U.S. 398, 418 (2007), *quoting In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006). "'[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated

reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *Id.* The Court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419; *see also id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue").

Here, the Examiner has failed to correctly identify any reason why one of ordinary skill in the art would combine elements of the prior art to arrive at the claimed invention. The Examiner relies on a selective reading of the prior art to arrive at the unsupported conclusion that as "one skilled in the art could have combined the elements with no change in their respective functions, and the combination would have yielded predictable results." The lack of support for such a conclusions it is clear the Examiner has used the instant specification as a blueprint for the rationale combine the prior art to arrive the instant claims. Such hindsight reconstruction is improper. For this reason additionally, all pending obviousness rejections should be withdrawn.

* * *

CONCLUSION

For the reasons set forth above, appellant request that the Board reverse the rejections of claims 22-24.

Dated: November 2, 2009

Respectfully submitted,

By /Mitchell Bernstein/
Mitchell Bernstein
Registration No.: 46,550
DARBY & DARBY P.C.

P.O. Box 770
Church Street Station
New York, New York 10008-0770
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

APPENDIX A- Claims Appendix

(37 C.F.R. § 41.37(c)(1)(viii))

1-21. (Cancelled)

22. (Previously presented) A method for reducing shedding of *E. coli* O157:H7 in an animal which comprises administering by parenteral injection to the animal an effective amount of a vaccine composition, wherein the vaccine composition comprises inactivated or killed whole *E. coli* O157:H7, an adjuvant and aluminum hydroxide, and optionally a pharmaceutically acceptable carrier;

wherein said adjuvant is an oil emulsion comprising:

(a) 1% to 3% vol/vol of polyoxyethylene-polyoxypropylene block copolymer;

(b) 2% to 6% vol/vol of squalane;

(c) 0.1% to 0.5% vol/vol of polyoxyethylene sorbitan monooleate; and

(d) buffered salt solution.

23. (Previously presented) The method according to Claim 22 which further comprises administering an effective amount of *Lactobacillus acidophilus* or neomycin medicated feed supplement to the animal.

24. (Previously presented) The method according to Claim 22 wherein said method produces minimal injection site reaction.

APPENDIX B- Evidence Appendix

(37 C.F.R. § 41.37(c)(1)(ix))

Attached as evidence is a copy of A Declaration Under 37 C.F.R. §1.132 by Wumin Li ("the Li Declaraction") that is relied upon by Appellant in the appeal. The Li Declaration was submitted on July 9, 2007. The Examiner indicated that the Li Declaration had been considered in a non-final Office Action that was mailed on September 18, 2007, see page 2, section entitled "Declaration."

Other than the Li Declaration, no evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the examiner is being submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Attorney Docket No. AM101333)

In re Patent Application of:	)	Appln. No.: 10/796,925
	)	Confirmation No.: 3270
WUMIN LI *et al.*	)	Customer No.: 25291
	)	Group Art Unit: 1645
Filed: 03/10/2004	)	Examiner: Lakia J. Tongue
	)	
For: ADJUVANTED BOVINE VACCINES	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

I, WUMIN LI, declare and say as follows:

THAT I am the same WUMIN LI who is named as co-inventor with HSIEN-JUE (STEVE) CHU in the above-referenced application for United States Letters Patent;

THAT I currently hold the position of Senior Manager, Biological Research and Development at Fort Dodge Animal Health in Fort Dodge, IA since 2003 to present date;

THAT I previously held the position of Manager, Biological Research and Development at Fort Dodge Animal Health from 1999 to 2003 and the position of Project Leader as a research scientist at Fort Dodge Animal Health from 1995 to 1999;

THAT I had been employed as a research scientist at Pfizer Animal Health, Groton, Connecticut from 1993 to 1995;

THAT I received the degrees of Masters of Science in Veterinary Science in 1989 and Doctor of Philosophy in Veterinary Science in 1993 from the University of Wisconsin-Madison, Department of Animal Health and Biomedical Sciences, Madison, WI;

THAT I am familiar with the above-said application and do understand the Official action of March 8, 2007 pertaining thereto;

THAT the following experiment was conducted at my behest and on my behalf to demonstrate that the *E. coli* O157:H7 vaccine formulation of the present invention provides an unexpectedly safe injectable formulation that elicits a markedly effective immune response.

Experiment

Evaluation of Serological Response and Safety of *E. Coli* O157:H7 Vaccine in Cattle

A side-by-side comparison study was performed to evaluate the serological response and safety of test *E. coli* O157:H7 vaccines in cattle following vaccination. Control Group 1 remained unvaccinated during the experiment. Only the adjuvant varied between the two test vaccine groups. Group 2 was vaccinated with an *E. coli* O157:H7 vaccine containing a standard adjuvant that consisted of aluminum hydroxide (art-recognized as a conventional vaccine adjuvant). Group 3 was vaccinated with an *E. coli* O157:H7 vaccine containing the novel metabolizable oil adjuvant of the present invention that comprised aluminum hydroxide and SP Oil. As used in the experiment and the application, the term "SP Oil" designates an oil emulsion comprising a polyoxyethylene-polyoxypropylene block copolymer, squalane, polyoxyethylene sorbitan monooleate (Tween 80, an emulsifier) and a buffered salt solution.

Twenty-four healthy mixed breed cattle obtained from commercial sources were used in the study. Their age range was 6 – 12 months at first vaccination, and both male and female animals were used. The cattle were group housed in housing meeting applicable animal welfare regulations. Water and food were available *ad lib.* All animals were treated as deemed necessary by the plant veterinarian after consultation with the study director. Treatments before and during the study were documented. Animals requiring antibiotics or potentially immunosuppressive drugs were removed from the study.

Vaccine compositions were formulated and tested for sterility and laboratory animal safety as specified in 9 C.F.R. §§ 113.26 and 113.33. Vaccines were stored at 2-7°C. Calves were randomly divided into groups of six animals each. Group 2 was vaccinated with the test vaccine containing the conventional adjuvant. Group 3 was vaccinated with the test vaccine containing the unique metabolizable oil adjuvant in accordance with the present invention. Group 1 was held as unvaccinated controls. Calves were vaccinated with a 2 mL dose of the appropriate vaccine by the subcutaneous route. A second dose was administered in 3-4 weeks, and a third dose was administered after a further 3-4 weeks. Calves were bled at the time of the first and second dose, and then weekly thereafter until four weeks post third vaccination. Each serum sample was evaluated for antibody response.

Serum analysis was done by statistical methods to determine differences in antibody response. ELISA titers were determined to assess vaccine response, and results were averaged. Injection sites were observed for three days following each vaccination. If any injection site reactions were seen, the cattle were then observed up to 14 days post vaccination or until the reaction had dissipated. Injection site reactions were measured in three dimensions (length, width and height). A daily reaction score was calculated by L x W x H. Total reaction scores were analyzed by Mann Whitney Rank Sum. The level of significance was set at $p<0.05$.

ELISA titer results are shown in the following Table 1.

Table 1: ELISA Titer Results of Serology Testing

Vaccine Group*	**Calf Number**	**0 Days Post First Vaccination**	**14 Days Post Third Vaccination**
1	283	640	1280
1	291	640	640
1	367	640	640
1	368	640	640
1	369	640	640
Average (1)		640	735
2	389	640	640
2	277	640	640
2	292	2560	2560
2	379	320	640
Average (2)		735	868
3	390	640	1280
3	384	1280	2560
3	294	320	1280
Average (3)		573	1184

* Vaccine Groups: Group 1 = control; Group 2 = standard adjuvant; and Group 3 = SP Oil/AlOH adjuvant of present invention.

Injection site reactions are shown in the following Table 2.

Table 2: Reaction Scores Assessing Injection Site Reactions

Vaccine Group*	-1dpv2**	0dpv2	1dpv2	2dpv2	3dpv2	4dpv2	5dpv2
1	0	0	0.0	0.0	0.0	0.0	0.0
2	0	0	68.4	58.0	31.9	30.8	19.0
3	0	0	25.4	61.5	43.3	52.1	61.3

Vaccine Group*	6dpv2	7dpv2	10dpv2	11dpv2
1	0.0	0.0	0.0	0.0
2	9.8	10.1	6.6	1.5
3	24.9	15.3	1.2	2.8

* Vaccine Groups:
Group 1 = control;
Group 2 = standard adjuvant; and
Group 3 = SP Oil/AlOH adjuvant of present invention.

** Heading definitions:
-1dpv2 = assessment of injection site on day before second vaccination
0dpv2 = assessment of injection site on day of second vaccination
1dpv2 = assessment of injection site one day post second vaccination
2dpv2 = assessment of injection site two days post second vaccination
3dpv2 = assessment of injection site three days post second vaccination
4dpv2 = assessment of injection site four days post second vaccination
5dpv2 = assessment of injection site five days post second vaccination
6dpv2 = assessment of injection site six days post second vaccination
7dpv2 = assessment of injection site seven days post second vaccination
10dpv2 = assessment of injection site ten days post second vaccination
11dpv2 = assessment of injection site eleven days post second vaccination

The above ELISA titer results in Table 1 demonstrate that the animals of Group 3 surprisingly showed significantly enhanced immunogenic responses over those of Group 2 and the control group based on the levels of the ELISA titers fourteen days post third vaccination.

Insofar as the variation in a few titers is concerned, it is explained that some abnormalities are to be expected under the circumstances of working with live animals. Applicants utilized a good control facility and exercised care during the experiment. However,

E. coli is ubiquitously found. The calves that had a high titer before injection (calf # 292) or had an increased titer without treatment (calf # 283) might have been infected with another *E. coli* strain and peaked as a cross-reaction despite the attempt to keep the controls clean of infection; or perhaps one of the calves had been exposed accidentally to *E. coli* O157:H7. Any practitioner who works in the veterinary field with cattle would appreciate these and other possible reasons for certain titers to be anomalous.

The more important value of the titers in Table 1 is seen in the overall average of each group of animals involved in the study, namely, a significantly improved titer of 1184 for those treated by the vaccine formulation of the invention (Group 3) as compared to 868 for those animals treated by the vaccine containing the conventional adjuvant (Group 2) and further compared to 735 for the controls (Group 1). By and large, the controls stayed at the baseline titer of 640 (a normal range) and the titers of the conventionally adjuvanted vaccine remained the same over time. Yet, unexpectedly, it was observed that the vaccine composition of the invention (metabolizable oil plus aluminum hydroxide) demonstrated a significant improvement in titers over the standard adjuvant (aluminum hydroxide) used in the comparative vaccine.

Considering the significantly higher immunogenic responses in Group 3 of the present invention, the above reaction scores in Table 2 revealing similar rates of injection site reactions to the two test vaccines on comparison and the noteworthy observation of no major reaction after inoculation with the vaccine of the invention were not anticipated. With all vaccinations, a little lump is to be expected when the active ingredient is released slowly from the site of depot administration but vaccines that give a significantly higher immune response typically cause a much greater site reaction that is deleterious to meat quality. Because severe lumps usually form from potent vaccines, it was presumed that the vaccine composition having the higher host immune response would cause a greater adverse reaction, which would adversely impact the meat quality of the animals sold for food consumption. It was unexpected, therefore, to observe that the size of the reaction lump of the vaccine of the invention was the same as a traditional vaccine formulation and the animals of both test groups displayed minimal, normal injection reactions at the vaccine administration sites.

As can be seen by the above experiment, the results establish that the vaccine of the present invention is able to stimulate the host immune system and elicit a potent immune response against *E. coli* O157:H7. The data showed that the vaccine formulation of the present invention provided the greatest overall serological titers to *E. coli* O157:H7 as compared to a standard vaccine formulation of the art and the placebo group (the control). Since there is a direct correlation between antibody titer and vaccine efficacy, the superior host serological response clearly establishes that the vaccine containing the metabolizable oil adjuvant of the invention would beneficially induce active immunity against *E. coli* O157:H7, prevent colonization of *E. coli* O157:H7, provide bactericidal effect and, consequently, reduce shedding in cattle.

The results also substantiate that the *E. coli* O157:H7 vaccine composition containing the metabolizable oil adjuvant is safe for immunizing food animals. The unpredictable reaction scores in light of the serological testing prove that the vaccine of the invention provides beneficial biological activity and a practical advantage over the traditional vaccine formulation in being highly effective yet safe on administration to cattle.

I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with knowledge that willful, false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 06 July 07 By: Wumin Li

WUMIN LI, Ph.D.

APPENDIX C- Related Proceedings Appendix

(37 C.F.R. § 41.37(c)(1)(x))

No related proceedings are referenced in section II, supra. Hence copies of decisions in related proceedings are not provided.